Palonosetron (Aloxi): a second-generation 5-HT_3 receptor antagonist for chemotherapy-induced nausea and vomiting

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In July 2003, the Food and Drug Administration approved palonosetron hydrochloride injection for the treatment of chemotherapy-induced nausea and vomiting (CINV). The newest agent in the class of 5-HT_3 receptor antagonists (5-HT_3RAs), palonosetron differs from other agents in its class by its higher receptor-binding affinity and longer half-life. These pharmacological properties have resulted in improved antiemetic activity in clinical trials, particularly in the treatment of delayed CINV following moderate emetogenic chemotherapy. Based on the results of these clinical studies, palonosetron is the only 5-HT_3RA approved for delayed CINV. Palonosetron is given as a single 0.25-mg intravenous dose 30 minutes before the initial dose of chemotherapy. Headache and constipation were the most common adverse events reported with palonosetron therapy.

Chemotherapeutic agents trigger the process of emesis through activation of multiple neurotransmitter receptors in the vomiting center of the brain, chemoreceptor trigger zone, and gastrointestinal tract (1). Pharmacological treatment of chemotherapy-induced nausea and vomiting (CINV) has focused on blocking these receptors using agents such as antihistamines (e.g., diphenhydramine), phenothiazines (e.g., promethazine, prochlorperazine), benzodiazepines (e.g., lorazepam), and corticosteroids (e.g., dexamethasone, methylprednisolone).

Significant strides were made in the 1990s for the treatment of CINV with the advent of selective 5-HT_3 receptor antagonists (5-HT_3RAs). Chemotherapeutic agents release serotonin from the enterochromaffin cells of the small intestine; this released serotonin is free to activate 5-HT_3 receptors located on peripheral vagal nerve terminals and centrally in the chemoreceptor trigger zone, resulting in the initiation of the vomiting reflex.

Even with several drugs in the 5-HT_3RA class available, the incidence of acute and delayed CINV remains high. Grunberg and colleagues studied patients who were treated according to current antiemetic guidelines after receiving moderate emetogenic chemotherapy (MEC) to highly emetogenic chemotherapy (HEC). Almost all patients (97%) received a 5-HT_3RA, and 78% also received a corticosteroid. Two or more antiemetics were given to 80% of patients. Treatment was generally given during both acute- and delayed-risk phases of nausea and vomiting. During the acute phase (<24 hours after the first dose of chemotherapy), 35% of patients experienced acute nausea and 13% of patients experienced acute vomiting. During the delayed phase (>24 hours after the first dose of chemotherapy), 60% of patients receiving HEC experienced nausea and 50% experienced vomiting, while 52% of patients receiving MEC experienced nausea and 38% experienced vomiting (2). Nausea and vomiting, particularly in the delayed phase, continue to be significant problems for patients receiving chemotherapy.

Palonosetron, the newest agent in the 5-HT_3RA class of drugs, has a strong binding affinity to 5-HT_3 receptors and thus selectively blocks serotonin from binding to these receptors peripherally and centrally. It has little or no affinity for other receptors. Palonosetron is indicated for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderate to highly emetogenic cancer chemotherapy.

PHARMACOKINETICS

Compared with earlier 5-HT_3RAs, palonosetron has unique pharmacokinetic properties. After administration in healthy subjects and cancer patients, slow elimination from the body occurs after an initial decline in plasma levels. Palonosetron has a volume of distribution of approximately 8.3 ± 2.5 L/kg, with approximately 62% bound to plasma proteins. Approximately 50% of palonosetron is metabolized into two inactive metabolites that exhibit <1% of the 5-HT_3RA activity. Palonosetron is metabolized via the CYP2D6 enzyme pathway and to a lesser extent, CYP3A and CYP1A2 enzyme pathways. After a single intravenous dose, approximately 40% is excreted as unchanged drug in the urine after 144 hours. Total body clearance of palonosetron was 160 ± 35 mL/h/kg, and renal clearance was 66.5 ± 18.2 mL/h/kg in healthy subjects. When compared with other agents in the class, palonosetron exhibits a longer half-life (40 hours) and has a greater 5-HT_3 receptor binding affinity (3).

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CLINICAL TRIALS

Three trials were conducted to compare the efficacy of palonosetron with that of other 5-HT_3RA agents. Two studies evaluated palonosetron use prior to MEC, and one study evaluated palonosetron use prior to HEC.

Study 1

Gralla and colleagues conducted a multicenter, randomized, double-blind, stratified study of 570 adult patients that received either a single intravenous dose of palonosetron 0.25 mg, palonosetron 0.75 mg, or ondansetron 32 mg 30 minutes before administration of MEC (4). The primary endpoint was complete response (CR) established as the proportion of patients without emetic episodes and rescue medication during the acute phase (<24 hours after the initial dose of chemotherapy). Secondary endpoints included efficacy of treatment of delayed phase (>24 hours but <120 hours after the initial dose of chemotherapy) and overall CR (0 to 120 hours after the initial dose of chemotherapy). Compared with ondansetron 32 mg, palonosetron 0.25 mg achieved significantly higher CR rates (81% vs 68.6%, respectively; $P < 0.01$) during the acute phase. Statistically significant results were also observed in delayed-phase CR (74.1% vs 55.1%, $P < 0.001$) and overall CR (69.3% vs 50.3%, $P < 0.001$). Palonosetron 0.75 mg did not demonstrate a statistically significant advantage in efficacy compared with palonosetron 0.25 mg. Based on the results, the authors concluded that a single intravenous dose of palonosetron 0.25 mg was superior to a single intravenous dose of ondansetron 32 mg in the prevention of acute and delayed CINV after administration of MEC.

Study 2

A study conducted by Eisenberg and colleagues (5) comparing palonosetron with dolasetron revealed similar results. The study included 569 patients in an intent-to-treat, multicenter, randomized, double-blind, parallel, stratified, comparative trial evaluating efficacy after administration of MEC. Each patient was randomized to receive a single dose of palonosetron 0.25 mg, palonosetron 0.75 mg, or dolasetron 100 mg intravenously 30 minutes before the administration of chemotherapy. The established endpoints were CR during the acute phase (<24 hours) and delayed phase (24 to 120 hours) of nausea and vomiting and overall CR (0 to 120 hours). Compared with dolasetron 100 mg, palonosetron 0.25 mg achieved higher CR rates in the acute phase (63% vs 52.9%, $P = 0.049$), delayed phase (54% vs 38.7%, $P = 0.004$), and overall (46% vs 34%, $P = 0.021$). The higher CR rates for palonosetron 0.75 mg were not statistically significant in the acute phase (57.1%, $P = 0.412$) but were statistically significant in the delayed phase (56.6%, $P < 0.001$) and overall (47.1%, $P = 0.012$). The authors concluded that a single intravenous dose of palonosetron 0.25 mg prior to MEC was as effective as a single intravenous dose of dolasetron 100 mg for the prevention of acute CINV but was more effective in preventing delayed CINV.

Study 3

A third trial conducted by Aapro and colleagues (6) evaluated the efficacy of palonosetron and ondansetron combined with a corticosteroid prior to HEC. The study included 447 patients in a randomized, double-blind, parallel, comparative trial. Each patient received a single dose of either palonosetron 0.25 mg or ondansetron 32 mg intravenously, with 67% of patients also receiving corticosteroids in each study group. Primary endpoints were CR during both the acute phase and overall. The difference in CR between palonosetron and ondansetron during the acute phase was not statistically significant (64.7% vs 55.8%); however, palonosetron was significantly better (40.7% vs 25.2%, 97.5% CI) when overall CR was evaluated. The authors concluded that a single intravenous dose of palonosetron 0.25 mg prior to HEC was as effective as a single intravenous dose of ondansetron 32 mg in preventing acute CINV and more effective in preventing delayed CINV.

POSITION OF PALONOSETRON IN CLINICAL GUIDELINES

Recommendations for antiemetic therapy in patients receiving chemotherapy are outlined both by the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) in their respective 2006 guideline updates. Many clinical studies comparing all commercially available 5-HT_3RAs have been conducted using various routes, dosing ranges, and dosing schedules (7–9). Both the NCCN and ASCO agree that studies have demonstrated that all 5-HT_3RAs are equally efficacious in equivalent doses in preventing acute CINV with minimal adverse events and recommend the use of a 5-HT_3RA, corticosteroids, and/or aprepitant for prevention of acute emesis with MEC and HEC (10, 11). A specific combination of agents is further defined with respect to the emetic risk category of the antiemetic therapy.

Neither set of recommendations selected a 5-HT_3RA as a preferred agent, although differences in the pharmacology and pharmacokinetic parameters of the agents do exist. Because palonosetron exhibits significantly different pharmacodynamics than the other 5-HT_3RAs and is the only 5-HT_3RA approved for delayed CINV, the NCCN suggests the use of a single dose of palonosetron for 3-day chemotherapy regimens instead of daily oral or intravenous 5-HT_3RAs. The use of daily or more frequent dosing of palonosetron in longer multiple-day chemotherapy regimens has not been established and is not recommended despite palonosetron's safety profile at high doses. ASCO recognizes that palonosetron outperformed other 5-HT_3RAs in comparative studies; however, the primary endpoints only established noninferiority. The lack of relevant studies to test the superiority of palonosetron combined with other agents as standard of care in treating CINV has led ASCO to suggest that palonosetron is only equally efficacious to other 5-HT_3RAs in equivalent doses.

CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS

Palonosetron is contraindicated in patients with a known hypersensitivity to the compound or any of its components. Palonosetron should be administered with caution in patients

Table 1. Adverse reactions occurring ≥2% in any treatment group from studies evaluating chemotherapy-induced nausea and vomiting*

Event	Palonosetron 0.25 mg (N = 633)	Ondansetron 32 mg (N = 410)	Dolasetron 100 mg (N = 194)
Headache	9%	8%	16%
Constipation	5%	2%	6%
Diarrhea	1%	2%	2%
Dizziness	1%	2%	2%
Fatigue	<1%	1%	2%
Abdominal pain	<1%	<1%	2%
Insomnia	<1%	1%	2%

*Modified with permission from reference 12.

Table 2. Daily average wholesale price comparison of 5-HT_3 receptor antagonists

5-HT_3 receptor antagonist	Intravenous dose (mg)	Cost/day
Ondansetron (Zofran)*	24	$98.44
	32	$131.26
Dolasetron (Anzemet)	100	$48.75
Granisetron (Kytril)†	1	$195.20
Palonosetron (Aloxi)	0.25	$372.00‡

*Based on price of $164.07 per 40-mg multidose vial.
†Based on price of $780.80 per 4-mg multidose vial.
‡Cost reflects one-time dose only since multiple doses of palonosetron have not been studied in multiple-day chemotherapy regimens.

who have or may develop prolongation of cardiac conduction intervals, particularly QTc. Such patients include those with hypokalemia or hypomagnesemia, patients taking diuretics with the potential for inducing electrolyte abnormalities, patients with congenital QT syndrome, patients taking antiarrhythmic drugs or other drugs that lead to QT prolongation, and patients receiving cumulative high-dose anthracycline therapy (12).

There are no adequate, well-controlled studies of the use of palonosetron in pregnant women; however, teratology studies performed in rats given oral doses of 60 mg/kg/day have not revealed evidence of impaired fertility or harm to the fetus. Although the dose tested in rats represents 1894 times the recommended human intravenous dose based on body surface area, animal studies are not always predictive of human response. Therefore, palonosetron should be used during pregnancy only if clearly needed. Palonosetron is designated as a category B agent.

ADVERSE EVENTS

The most commonly reported adverse reactions with the use of palonosetron were headache and constipation. *Table 1* compares adverse reactions reported by ≥2% of patients during clinical trials with palonosetron, ondansetron, and dolasetron. Adverse reactions were similar in severity and frequency with all three drugs.

DRUG INTERACTIONS

Palonosetron has only a minor effect on the cytochrome P450 pathway. No drug interactions have been reported related to enzyme induction or inhibition; however, concurrent use of apomorphine may result in profound hypotension and altered consciousness and is contraindicated (13).

DOSING AND ADMINISTRATION

The manufacturer-recommended dosage is 0.25 mg administered intravenously as a single dose over 30 seconds approximately 30 minutes prior to the administration of chemotherapy on day 1 of each cycle. Doses should not be given more than once weekly due to a lack of studies evaluating the safety and efficacy of repeat multiple dosing of palonosetron. A recommended intravenous dose for pediatric patients has not been established. No dosage adjustment is needed for geriatric patients or for patients with renal or hepatic impairment (14).

Palonosetron hydrochloride injection is currently available as a solution in a single-use 5 mL vial containing 0.25 mg (0.05 mg/mL). An oral formulation of palonosetron is currently in phase III trials and if approved for marketing will provide health care professionals an option of intravenous or oral administration to patients.

PHARMACOECONOMICS

Due to the increasing cost of care for cancer patients, cost-effectiveness continues to be a major concern when choosing therapeutic agents. Proper dosage, length of therapy based on multiple-day chemotherapy regimens, the emetic potential of the chemotherapeutic agents, and patient history of response to 5-HT_3RAs with previous cycles of chemotherapy are important factors to consider when choosing agents within the class. However, because national guidelines have established all 5-HT_3RAs to be equally effective for the prevention of CINV, the acquisition cost by the institution becomes the driving force for which agent will become the preferred formulary 5-HT_3RA. *Table 2* provides a cost comparison based on average daily dose of all 5-HT_3RAs.

CONCLUSIONS

Clinical studies clearly establish that palonosetron is as effective as other 5-HT_3RAs in the prevention of acute CINV and is more effective in the prevention of delayed CINV. However, with the importance of minimizing the cost of cancer treatment, more studies are needed to evaluate the effectiveness of palonosetron compared with other 5-HT_3RAs using standard of care combination therapy with corticosteroids and aprepitant. Further studies are needed as well to evaluate the use of palonosetron in multiple-day chemotherapy regimens. Until these data become available, health care systems will continue to use the most cost-effective 5-HT_3RA for their oncology patients and may reserve palonosetron use for patients who are refractory to less expensive agents in the class.

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